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(21) International Application Number: PCT/GB93/02035 (22) International Filing Date: 30 September 1993 (30.09.93) (30) Priority data: 9221743.9 16 October 1992 (16.10.92) GB (71) Applicant (for all designated States except US): IMPERIAL CHEMICAL INDUSTRIES PLC [GB/GB]; Imperial Chemical House, Millbank, London SW1P 3JF (GB). (72) Inventors; and (75) Inventors/Applicants (for US only) : GARNIER, Laurent [FR/FR]; 13, allée du Trou-Normand, F-95330 Domont (FR). BURDON, James [FR/FR]; 66 Chesterwood Road, Kings Heath, Birmingham B13 0QE (FR). PO- WELL, Richard, Llewellyn [GB/GB]; 9 Sadler's Wells, Bunbury, Tarporley, Cheshire CW6 9NV (GB).		(74) Agents: OLDROYD, Alan et al.; ICI Group Patents Ser- vices Dept., P.O. Box 6, Shire Park, Welwyn Garden City, Hertfordshire AL7 1HD (GB). (81) Designated States: CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: PRODUCTION OF PARTIALLY FLUORINATED ETHERS (57) Abstract A process for the fluorination of a partially fluorinated ether having the formula $R-O-CH_2-R^1$ wherein R is a fluoroalkyl group having from 1 to 6 carbon atoms and R^1 is hydrogen, fluorine or a fluoroalkyl group having from 1 to 6 carbon atoms, provided that where R^1 is a fluoroalkyl group, R is not a trifluoromethyl group or a fluoroalkyl group having a difluoromethylene group at the α -position relative to the oxygen atom, which comprises contacting the partially fluorinated ether with a transition metal fluorinating agent, especially cobalt trifluoride. 1-difluoromethoxy-1,2,2,2-tetrafluoroethane may be produced where the fluorinated ether has the formula $CF_3-CHR-O-CH_2R$ where each R is independently fluorine or hydrogen.		

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PRODUCTION OF PARTIALLY FLUORINATED ETHERS.

This invention relates to a process for the production of higher partially fluorinated ethers, in particular

5 1-difluoromethoxy-1,2,2,2-tetrafluoroethane, from lower partially fluorinated ethers, that is a process for the fluorination of partially fluorinated ethers.

1-difluoromethoxy-1,2,2,2-tetrafluoroethane, commonly known and hereafter referred to as
10 "Desflurane" is known to have valuable anaesthetic properties but processes previously proposed for its production have suffered from various disadvantages relating to the availability and toxicity of starting materials with resulting scale-up problems for the
15 production of commercial quantities.

It has recently been proposed in European Patent Publication No. 0 482 936 to produce Desflurane by the fluorination of
1-difluoromethoxy-2,2,2-trifluoroethane under
20 relatively mild conditions in the vapour phase using a transition metal fluorinating agent, in particular cobalt trifluoride.

However, 1-difluoromethoxy-2,2,2-trifluoroethane is itself not readily prepared and the yields of
25 Desflurane obtained by the process are not as high as may be desired, the main by-products being over-fluorinated materials which cannot therefore be further fluorinated to desflurane.

We have now found that lower fluorinated ethers
30 (lower fluorine content) than 1-difluoromethoxy-2,2,2-trifluoroethane can be fluorinated using a transition metal fluorinating agent to give substantial yields of Desflurane and by-products which may be further fluorinated to
35 Desflurane. Furthermore, such lower fluorinated

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ethers are much more readily prepared than is 1-difluoromethoxy-2,2,2-trifluoroethane.

According to the present invention there is provided a process for the fluorination of a partially fluorinated ether having the formula:



wherein R is a fluoroalkyl group having from 1 to 6 carbon atoms and R¹ is hydrogen, fluorine or a fluoroalkyl group having from 1 to 6 carbon atoms, provided that where R¹ is a fluoroalkyl group, R is not a trifluoromethyl group or a fluoroalkyl group having a difluoromethylene group at the α -position relative to the oxygen atom, which comprises contacting the fluorinated ether with a transition metal fluorinating agent.

Preferably the group R comprises a partially fluorinated alkyl group having no more than one fluorine atom attached to the carbon atom at the α -position relative to the oxygen atom, and more preferably the group R comprises a 2,2,2-trifluoroethyl or 1,2,2,2-tetrafluoroethyl group.

Preferably R¹ is a hydrogen or fluorine atom or a trifluoromethyl group, particularly a hydrogen or fluorine atom.

We especially prefer that the group R¹ is a fluorine or hydrogen atom and the group R is a 2,2,2-trifluoroethyl or 1,2,2,2-tetrafluoroethyl group, since these compounds readily yield Desflurane.

According to a preferred embodiment of the invention there is provided a process for the production of

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1-difluoromethoxy-1,2,2,2-tetrafluoroethane which comprises contacting a fluorinated ether having the formula



5 where each R is independently fluorine or hydrogen, with a transition metal fluoride fluorinating agent.

The starting fluorinated ethers of the preferred embodiment of the invention are therefore (i)

1,1,1-trifluoro-2-methoxyethane, $\text{CF}_3\text{CH}_2\text{-O-CH}_3$ (ii)

10 1,1,1-trifluoro-2-fluoromethoxyethane, $\text{CF}_3\text{CH}_2\text{-O-CH}_2\text{F}$,

(iii) 1,1,1,2-tetrafluoro-2-methoxyethane,

$\text{CF}_3\text{CHF-O-CH}_3$ and

(iv) 1,1,1,2-tetrafluoro-2-fluoromethoxyethane,

$\text{CF}_3\text{CFH-O-CH}_2\text{F}$.

15 We have found that Desflurane is produced with greater selectivity from these starting materials than when 1-difluoromethoxy-2,2,2-trifluoroethane, $\text{CF}_3\text{CH}_2\text{-O-CF}_2\text{H}$ is employed as the starting material.

20 The starting materials of the present invention may be readily prepared from commercially available materials. Thus, (i) may be prepared by the reaction of trifluoroethanol with dimethyl sulphate under basic conditions or by the reaction of methyl iodide with $\text{CF}_3\text{CH}_2\text{ONa}$ and (ii) may be prepared by the liquid
25 phase reaction of trifluoroethanol with a mixture of hydrogen fluoride and formaldehyde as described in our published International Patent Application No. WO 93/12057. (iii) and (iv) may be prepared as described in GB Patent No. 1537861, and DT-OS 23 40 560
30 referred to therein, or by the liquid phase reaction of methanol and fluoral hydrate respectively with a mixture of hydrogen fluoride and formaldehyde, as described in our published International Patent Application No. WO 93/12057.

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Cobalt trifluoride is the preferred transition metal fluoride fluorinating agent but other transition metal fluoride fluorinating agents which may be employed include, for example, the fluorides of manganese, silver and cerium or alkali metal complexes of the transition metal fluorides, for example potassium tetrafluorocobaltanate, potassium tetrafluoroargentate, and potassium hexafluoronickelate.

The temperature at which the process is effected will depend to some extent upon the fluorinating power of the particular fluorinating agent employed although usually the temperature will be in the range from about 150°C to about 450°C.

Where the fluorinating agent is cobalt trifluoride, the temperature is preferably in the range from about 180°C to about 280°C, especially from about 200°C to about 260°C.

The process is conveniently operated at about atmospheric pressure, although superatmospheric or subatmospheric pressure may be employed if desired.

The process of the invention is preferably carried out in the vapour phase. The ether is preferably vaporised over a bed of the transition metal fluorinating agent. A carrier gas may be employed, for example nitrogen.

The product ether may be readily purified, for example by fractional distillation.

The invention is illustrated but not limited by the following examples in which all % are mole %.

EXAMPLE 1.

6 kilogrammes of cobalt trifluoride were charged to an electrically heated nickel reactor vessel of

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length 96cm and diameter 16cm and was continually agitated by rotating nickel paddles.

The reactor was heated to a temperature of 250°C and 50g of 1,1,1-trifluoro-2-methoxyethane was passed over the catalyst in a stream of nitrogen with a flow rate of 5 litres per hour. The reactor off gases were collected in a Drikold-cooled copper vessel and the organics were separated from hydrogen fluoride by treatment with water at 0°C. 25g of organic product was collected. The organic product was sampled and analysed by gas chromatography. The organic product contained:

60% 2-difluoromethoxy-1,2,2,2-tetrafluoroethane,
23% 1-difluoromethoxy-2,2,2-trifluoroethane,
6% 1,1,1,2-tetrafluoro-2-fluoromethoxyethane and
6% 1-difluoromethoxy-1,1,2,2,2-pentafluoroethane.

EXAMPLE 2.

The procedure of example 1 was repeated except that the reactor was heated to 200°C. The organic product (16g) contained

57% 2-difluoromethoxy-1,2,2,2-tetrafluoroethane,
27% 1-difluoromethoxy-2,2,2-trifluoroethane,
5% 1,1,1,2-tetrafluoro-2-fluoromethoxyethane and
3% 1-difluoromethoxy-1,1,2,2,2-pentafluoroethane.

EXAMPLE 3.

The procedure of example 1 was repeated except that the ether passed over the cobalt trifluoride was 100g of 1,1,2,2-tetrafluoro-1-(2,2,2-trifluoroethoxy)ethane. The organic product (88g) contained:

CF₃CHFOCF₂CF₂H 66%
CF₃CH₂OCF₂CF₂H 14%

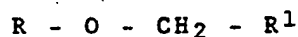
- 6 -

$\text{CF}_3\text{CH}_2\text{OCF}_2\text{CF}_3$	9%
$\text{CF}_3\text{CF}_2\text{OCF}_2\text{CF}_2\text{H}$	10%

CLAIMS.

1. A process for the fluorination of a partially fluorinated ether having the formula:

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wherein R is a fluoroalkyl group having from 1 to 6 carbon atoms and R¹ is hydrogen, fluorine or a fluoroalkyl group having from 1 to 6 carbon atoms, provided that where R¹ is a fluoroalkyl group, R is not a trifluoromethyl group or a fluoroalkyl group having a difluoromethylene group at the α -position relative to the oxygen atom, which comprises contacting the partially fluorinated ether with a transition metal fluorinating agent.

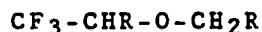
2. A process as claimed in claim 1 in which the group R comprises a 1,1,1-trifluoroethyl or 1,1,1,2-tetrafluoroethyl group.

3. A process as claimed in claim 1 or claim 2 in which R¹ is a hydrogen or fluorine atom or a trifluoromethyl group.

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4. A process for the production of 2-difluoromethoxy-1,1,1,2-tetrafluoroethane which comprises contacting a fluorinated ether having the formula

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where each R is independently fluorine or hydrogen, with a transition metal fluoride fluorinating agent.

5. A process as claimed in any one of claims 1 to 4 in which the transition metal fluorinating agent is cobalt trifluoride.

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6. A process as claimed in any one of claims 1 to 5
in which the temperature is in the range from about
100°C to about 450°C.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 93/02035

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 5 C07C43/12 C07C41/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,84 02909 (THE ELECTRICITY COUNCIL) 2 August 1984 see pages 13 and 21 ---	1-3,5,6
A	EP,A,0 482 938 (RHONE-POULENC CHEMICALS) 29 April 1992 see claims; examples -----	1-6

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-8402909	02-08-84	EP-A, B 0116417 GB-A, B 2133794 JP-T- 60500498 US-A- 4736045	22-08-84 01-08-84 11-04-85 05-04-88
EP-A-0482938	29-04-92	JP-A- 4273839	30-09-92